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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,293	04/05/2006	August Verbruggen	50304/014002	7006

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
08/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,293	VERBRUGGEN ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-63* is/are pending in the application.

4a) Of the above claim(s) *38-46 and 48-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/05/2006, 11/13/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II (claim 47) in the reply filed on 11/13/2007 is acknowledged. Claims 38-42 and 44-46 are linking claims, linking Groups I-V.

Claims 43 and 48-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/13/2007.

Claims 38-42 and 44-47 are pending and are under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38-42 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miraglia, *et al.* (1999, U.S. Patent 5,856,099, on Applicant's 04/05/2006 IDS), Monia, *et al.* (2001, U.S. Patent 6,309,882), Wahl, *et al.* (1987, Methods in Enzymology, v.152:399-407), and Kool (1997, U.S. Patent 5,683,874).

The claims are to a method for *in vitro* modulation of IL1RI gene expression by contacting fibroblast cells with 1-100 nM of an exon-bridging antisense oligonucleotide that has

a length of 15-30 nucleotides, a GC content of at least 45%, has a Tm of less than 32-36°C, and that bridges exons 02-03 in the mature mRNA of the IL1RI gene.

Miraglia, *et al.* teach antisense inhibition of IL1RI (abstract). The inventors teach that the preferred oligomers of their invention are 8-30 nucleobases in length and are specifically hybridizable to various regions of the target RNA, including the 5'-untranslated region (UTR), 3'-UTR, translation initiation site, 5' cap region, open reading frame, splice junction site, and exons and introns (column 3, lines 40-42 and top of column 7). Specifically, Miraglia, *et al.* claim a method of modulating the expression of IL1RI in cells *in vitro* comprising contacting the cells with an oligonucleotide hybridizable to RNA encoding IL1RI, wherein the oligonucleotide is SEQ ID NO: 32, which has a GC content of 65% (claim 19). At column 10, example 2, Miraglia, *et al.* indicate that fibroblast cells were treated with the antisense oligonucleotides at 50 and 100 nM concentrations (column 13, example 7). Miraglia, *et al.* do not specifically teach methods of using antisense oligomers that span the junction of exons 02 and 03 of the IL1RI gene. Miraglia, *et al.* do not explicitly teach methods of using antisense oligomers that have a Tm of less than 32-36°C.

It was well known at the time of the invention that preferred antisense oligonucleotide target sites were exon-exon junctions as taught by Monia, *et al.* Monia, *et al.* teach methods of inhibiting the expression of a gene (human replication protein A p70 subunit) comprising contacting cells *in vitro* with an antisense compound targeted to the gene (abstract and claims 1 and 12). At column 4, lines 45-50, Monia, *et al.* teach that preferred antisense oligonucleotide target sites are exon-exon junctions.

It was well known at the time of the instant application that the Tm of oligonucleotides depends on oligonucleotide length, sequence, mismatches, and salt concentrations of the

oligonucleotide solution and is readily determined by one skilled in the art (Wahl, *et al.*, p.401; Kool, column 10, last paragraph).

It would have been obvious to one of skill in the art at the time of the instant application to modulate IL1RI gene expression by contacting cells with an exon-bridging antisense oligonucleotide that bridges exons 02-03 in the mature mRNA of the IL1RI gene. Miraglia, *et al.* teach modulation of the IL1RI gene by contacting cells with antisense oligonucleotides targeting any portion of the RNA. Monia, *et al.* teach that preferred sites for antisense-mediated target gene inhibition are exon-exon junctions. Wahl, *et al.* and Kool provide evidence that it was well within the skill of those in the art to manipulate and determine oligonucleotide Tm. Provided the teachings of the references, one of skill in the art would immediately recognize that inhibiting IL1RI expression in cells *in vitro* could be accomplished by contacting cells with antisense oligomers that are complementary to IL1RI mRNA and, further, that particularly effective inhibition could be accomplished with oligonucleotides targeting the exon-exon junctions in the IL1RI mRNA sequence. One of ordinary skill in the art would have recognized that targeting exon-exon junctions with an antisense oligonucleotide would at least yield predictable results and, more likely, would yield improved results because Monia, *et al.* indicate that exon-exon junctions are preferred target sites for antisense oligonucleotide-mediated gene inhibition. Absent evidence to the contrary, the active step of inhibiting IL1RI by antisense oligonucleotide treatment of cells would result in the claimed (claim 45) increased synthesis of extracellular matrix compounds by the cells. Thus, the claims would have been *prima facie* obvious at the time of filing of the instant application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635